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Benign Proliferative Lesions Mimicking Recurrence of Hodgkin's Disease

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Salvage treatment in patients with recurrent Hodgkin's disease is more effective when tumor burden is minimal. That is why more intensive follow-up strategies, including frequent imaging tests, have been recently developed for the detection of early relapse. However, as screening procedures become more sensitive, there is an increasing risk of false-positive results, demonstrating nonmalignant proliferative disorders. We describe three young patients who had lymphocyte-predominant or mixed-cellularity Hodgkin's disease and were in clinical complete remission for 2.5–3 years after a combined treatment with chemotherapy and radiation. Imaging tests revealed new gallium-avid lymphadenopathy in the chest in two cases. Pathologically enlarged pelvic lymph nodes were identified in another case, after a diagnosis of recurrent disease in axilla. Those findings were interpreted as relapse, and the patients underwent thoracotomy and laparotomy, respectively, for histologic confirmation. The results showed progressively transformed germinal centers and sarcoid-like lesions, two benign proliferative disorders. When patients with Hodgkin's disease in remission show new lymphadenopathy, even with positive gallium scan, it seems mandatory to obtain tissue for histologic examination, even through invasive procedures such as laparotomy and thoracotomy, to avoid wrong diagnosis and unnecessary treatment. **Med. Pediatr. Oncol. 28:187–190**

Key words: Hodgkin's disease; recurrence; benign

INTRODUCTION

Patients with malignant lymphoma and Hodgkin's disease (HD) who relapse from complete remission (CR) may undergo salvage treatment with new aggressive regimens. It has been shown that those regimens are more effective in patients with minimal disease [1,2]. This has led to the design of more intensive follow-up strategies for patients achieving CR, aiming at the detection of preclinical relapse, when tumor burden is still low [3]. However, as screening procedures become more sensitive, there is an increasing risk of false-positive results, demonstrating nonmalignant processes. We have recently developed an intensive follow-up protocol for patients with malignant lymphoma and HD, consisting of frequent whole body computed tomography (CT) and gallium single photon emission computed tomography (SPECT) scans, which showed a high rate of early detection of recurrence [4]. However, we also described a case of gallium-67 uptake in a mass of benign transformation mimicking recurrence of HD [5].

We report our experience with three cases of Hodgkin's disease in remission, in which recurrence of disease was suspected based on the appearance of new mass lesions on CT scan with or without new abnormalities of gallium scintigraphy. Eventually, they proved not to indicate recurrence of the tumor, but represented benign proliferative activity.

CASE REPORTS

Patient 1

In 1989, a 31-year-old man was referred for clinical Stage IIIA nodular, lymphocytic-predominance HD (N-LPHD). He received six cycles of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) alternating with doxorubicin, bleomycin, and vinblastine (ABV) [6], combined with inverted-Y radiation therapy, 26 Gy. He achieved CR, documented by normalization of CT and gallium-67 scans. After 32 months of continuous clinical remission, a new focus of abnormal gallium-67 appeared in the right axillary region on a routine scan, and an enlarged right axillary lymph node was demonstrated on CT. The lymph node was then palpated and resected, and histologic study showed progressively transformed germinal centers (PTGC) with reactive follicular hyperplasia. Six months later, a CT scan showed new mediastinal and bilateral hilar adenopathy, which was also gallium-avid. Mediastinal lymph node biopsy by

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mediastinoscopy showed extensive infiltration by multiple epithelioid sarcoid-like granulomas with no evidence of HD. The large hilar masses on CT and intense uptake on gallium-67 scintigraphy were still worrisome, and it was not clear that the benign findings on the histology obtained by biopsy were not a local tissue reaction to adjacent site of active HD. Therefore, the patient underwent right open thoracotomy and biopsies of hilar nodes. Histology again showed prominent sarcoid-like granulomatous reaction obscuring the normal tissue intermingled with few foci of PTGC. Special stains like Ki-1 and Leu M1 for Reed–Sternberg cells, and L 26 and EMA for L&H cells, were negative. The patient remained well during a further follow-up period of 21 months, and CT and gallium scans became normal. Scintigraphic findings of this patient were described in detail by Bar-Shalom et al. [5].

Patient 2

In December 1990, a 32-year-old woman was admitted to the hospital for low back pain, low-grade fever, and weight loss. Abdominal CT scan revealed retroperitoneal paravertebral mass at the level of L4–5 and few enlarged retroperitoneal lymph nodes above. The mass contained purulent fluid that was drained by direct retroperitoneal approach. A biopsy of specimen of granulation tissue from inside the abscess showed mixed-cellularity (MC) HD. After staging investigations, the patient's disease was classified as clinical Stage II BE. CR, documented by normalization of CT and gallium-67 scans, was obtained during treatment with MOPP/ABV hybrid chemotherapy [6] combined with irradiation to para-aortic lymph nodes, completed in August 1991. In January 1994, a follow-up chest CT scan showed a new enlarged lymph-node in the azigo-esophageal recess. Gallium scan was positive and confirmed the new finding identified by CT. The same prominent findings were found on CT and gallium scintigraphy 3 months later and were clinically interpreted as relapse. There was no other evidence of disease, and the patient underwent thoracotomy and biopsy for histologic confirmation of HD. Biopsy revealed lymph nodes with epithelioid sarcoid-like granulomas (Fig. 1). Immunohistochemical studies did not provide evidence of HD.

Patient 3

A 33-year-old man was admitted to our lymphoma clinic in November 1985 with the diagnosis of HD, MC type, pathologic Stage IIA, having a bulky mediastinal mass and enlarged lymph nodes in both supraclavicular fossae. He was treated by six cycles of MOPP combination chemotherapy [6] followed by involved field irradiation to a dose of 40 Gy until June 1986. He achieved CR. The patient had no evidence of disease until the end of 1989, when a small lymph node was noticed in right axilla. On follow-up physical examination, there was no change in its size. It was removed in December 1991 and found to be involved with HD LP type [L 26(+), Leu M(−), Ki (1−)], whereas the previous MC type in 1985 showed Leu M(+) and Ki 1 (+). Restaging—including erythrocyte sedimentation rate (ESR), complete blood count, chemistry, whole body CT scan, gallium scan, and bone marrow biopsy—was negative. The patient then received irradiation, 40 Gy, to right axilla. Meanwhile, a lymphography was done and demonstrated an enlarged right common iliac lymph node and filling defects in a left common iliac lymph node. Repeat CT showed mild adenopathy in the right pelvis. In August 1992, the patient underwent diagnostic laparotomy. Biopsy of pelvic lymph nodes showed lymphatic hyperplasia with areas of PTGC, with no malignancy (Fig. 2). He was still disease free on last follow-up in December 1995.

DISCUSSION

PTGC was initially described by Lennert and Muller-Hermelink as enlarged reactive follicles composed predominantly of a diffuse infiltrate of small lymphocytes and an obscured mantle zone [7]. Several pathologists have evaluated the relationship between PTGC and HD. A review of the surgical pathology files of 171 cases of N-LPHD at Stanford University Medical Center revealed PTGC to coexist in the same lymph nodes in 18% of cases. In addition, PTGC was observed in lymph node biopsy specimens from two patients who subsequently developed N-LPHD. Moreover, three patients with histologically proven N-LPHD were found to have PTGC in subsequent lymph node biopsy [8].

In a retrospective study of 66 patients with the diagnosis of PTGC, Hansman et al. [9] found no association with HD in most patients. In 11 of these patients, however, an association with N-LPHD could be found; PTGC preceded or appeared simultaneously with HD in most cases. However, four patients, aged 17–29 years, had PTGC after the onset of N-LPHD. Three of them had a long history of a subsequent lymph node enlargement, with intervals of a few months up to 4 years. Lymph node enlargement with PTGC occurred in the same sites of HD or in other localizations. PTGC also could be found in other types of HD. It occurred before and during onset of MCHD in 2 of 96 patients. In 2 of 117 patients with nodular sclerosis (NS) HD, PTGC developed after the onset of the disease.

Osborne and Butler [10] evaluated 50 patients with PTGC for prior or subsequent development of HD. Thirty-one patients showed no association with HD. There were no patients who had PTGC preceding a diagnosis of HD, and five patients had concurrent PTGC and HD. However, 15 patients had a history of prior HD, which was LP in seven, nodular sclerosis (NS) in four, and MC in four. All were free of HD from 1 month to 10 years after PTGC biopsies.

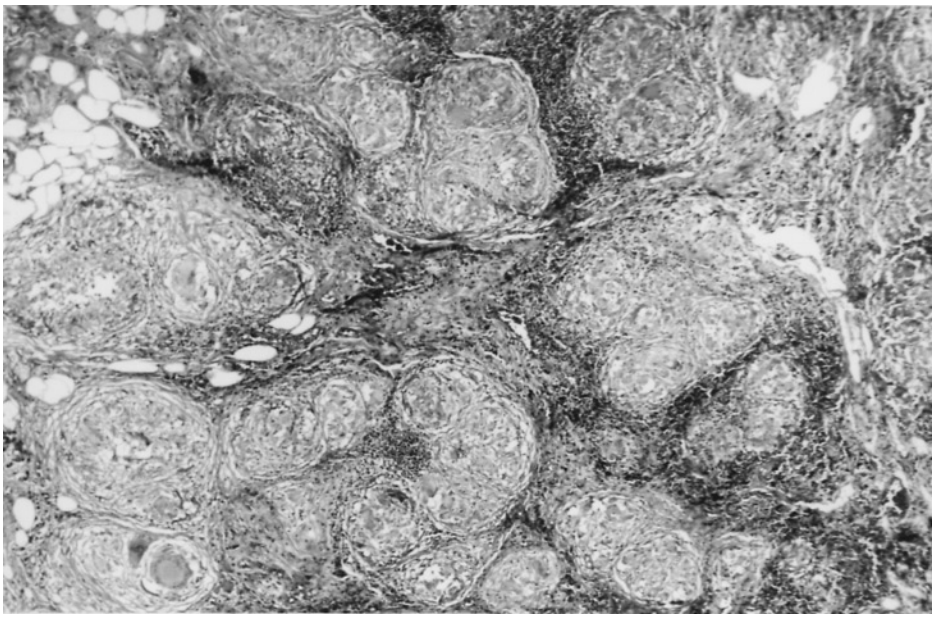

Fig. 1. A lymph node showing many sarcoid-like granulomas, composed of epithelioid-like cells and scattered giant cells. There is no infiltration by Hodgkin's disease. Hematoxylin-eosin, ×50.

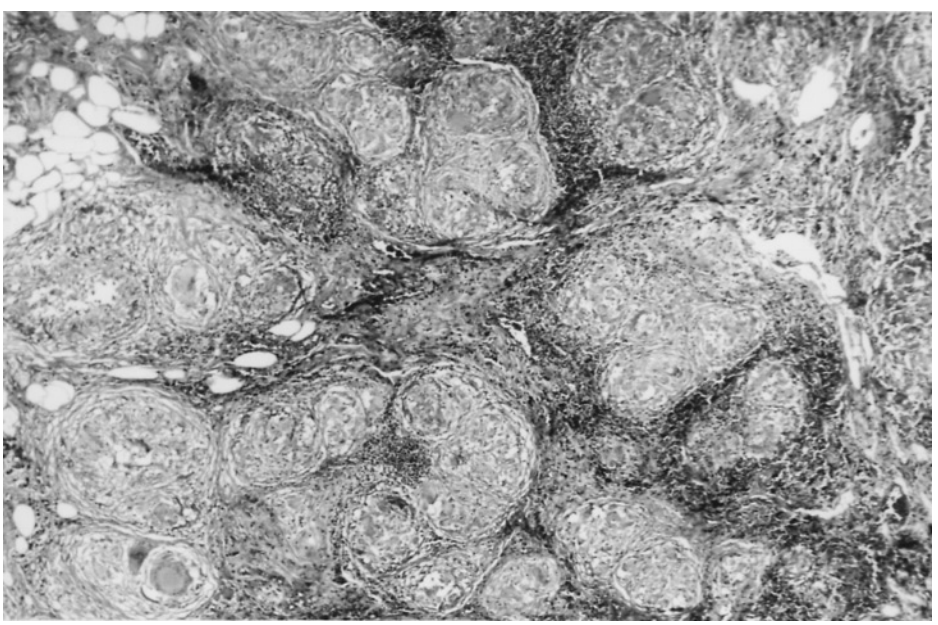

Fig. 2. A typical area showing in the center of large nodule characteristic of progressively transformed germinal centers in a background of follicular hyperplasia. Hematoxylin-eosin, ×100.

Immunologic studies demonstrated that PTGC and N-LPHD both affected the B-cell domains of the lymph node and may be related histogenetically. Popema et al. [11] proposed the concept of a gradual evolution from PTGC to N-LPHD. Others maintain that the finding of PTGC is not necessarily associated with HD activity, and the resemblance is more a superficial one [9,10].

Sarcoid reactions have been observed in association with different tumors. They occurred in 4.4% of patients with carcinomas, 7.3% of patients with non-Hodgkin's lymphoma (NHL), and 13.8% of patients with HD [12]. These reactions may occur in the tumor itself or in lymph nodes draining an area housing a malignant tumor; thus, they are considered to represent a local tissue reaction to

immediately adjacent active tumor. However, sarcoid-like granulomas may appear in nonregional and nonlymphatic tissue not affected by HD, suggesting that these epithelioid sarcoid-like granulomas may reflect a systemic host response to the tumor. This might even represent an increased immunologic defense reaction of the organism to HD, which may result in a favorable course for the patient [13]. O'Connell et al. [14] found granulomas in the liver and spleen in 17 of 91 patients with HD undergoing laparotomy. In their first retrospective study, they showed that these patients had an improved relapse-free survival compared with those without granulomas [14]. However, in a later follow-up, they reported that the survival advantage for patients with granulomas was no longer apparent [15]. A favorable clinical course for patients with high-grade NHL having extensive granulomatous reaction was reported by Hall et al. [16] and Hollingsworth et al. [17].

The reports in the literature describe sarcoidosis and sarcoid reaction appearing mostly before or concomitantly with the appearance of lymphoma [18–20]. Recently, Suen et al. [21] reviewed six patients with malignancy preceding sarcoidosis. In the four cases with lymphoproliferative disease, sarcoidosis occurred a median of 4 months after completion of therapy. The patients were asymptomatic or presented with dyspnea and cough, and all had bilateral lung infiltrates and/or hilar enlargement on chest radiography [21]. Sarcoid-like lesions may mimic relapse in cancer patients other than those with HD or NHL [21–23]. Sickles et al. [22] described two patients with uterine tumors in whom newly apparent intrathoracic masses were thought to represent recurrent disease. However, a biopsy specimen taken by mediastinoscopy showed benign findings characteristic of sarcoid [22]. Sorcoidosis mimicking recurrent disease was also described following breast and ovarian cancer [21] and testicular tumor [23].

In conclusion, PTGC and sarcoid-like granulomatosis in newly appearing lymph nodes in patients cured of HD reinforced the assumption that some activity of the lymphoproliferative system may appear or continue for years after tumor has been eradicated. While maintaining intensive follow-up procedures for early detection of relapse, we should be aware that new enlarged lymph nodes appearing during continuous clinical remission, even when gallim-avid, do not necessarily represent a true recurrence of HD; some benign changes may clinically mimic activity of lymphoma. Therefore, when using very sensitive follow-up methods, a biopsy should be performed—even through invasive procedures such as laparotomy and thoracotomy—to determine the nature of the lesion before initiating unnecessary salvage treatment.

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